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GB 2035350 A GB 1456775 A US 5262484 A
US 4283325 A

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(54) Graft-polymer biochemical compositions

(57) Polymeric biochemical compositions, particularly for medical and veterinary uses, comprise a graft copolymer prepared from a substantially hydrophobic thermoplastic polymer irradiation-grafted with one or more substantially hydrophilic ethylenically unsaturated comonomers, the composition containing one or more pharmaceutical compounds. The preferred graft copolymer is ethylene-vinyl acetate polymer grafted with acrylic and/or methacrylic acid.

In use, the compositions act as a polymeric reservoir for the rate controlled release of the pharmaceutical compound(s) to the required site.

One particular application is as a transdermal patch for the controlled release of nicotine in anti-smoking therapy or of other drugs, eg ibuprofen.

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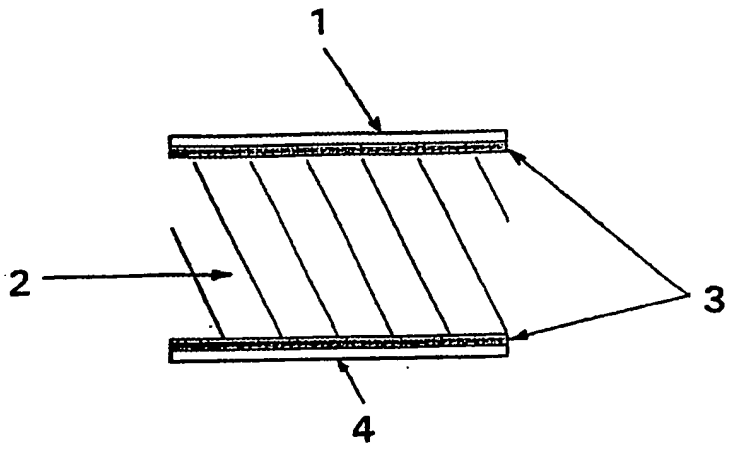
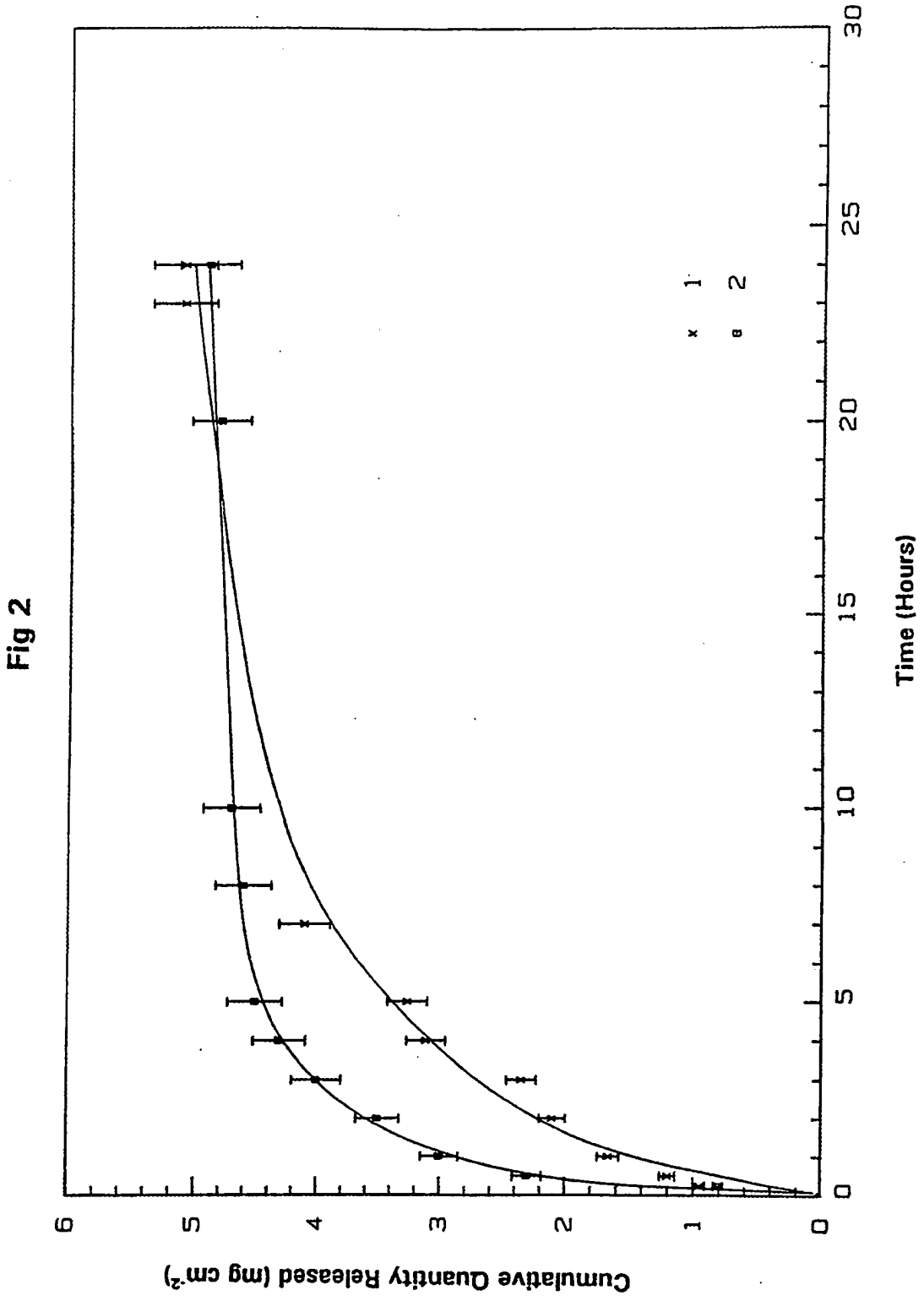
Fig 1

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1
2
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5
6
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5
10
15
20
25
30
1
2

Fig 2

Fig 3

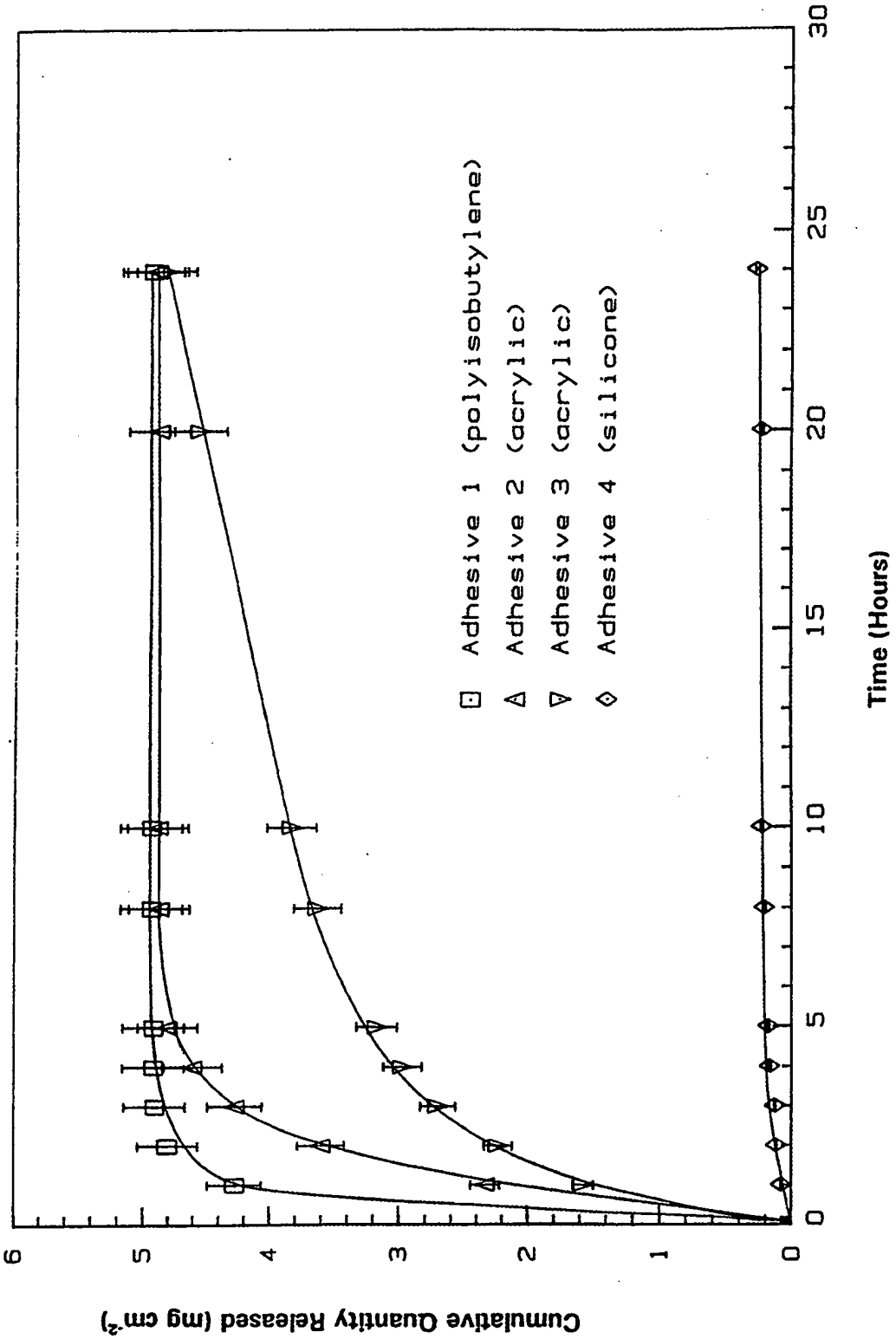
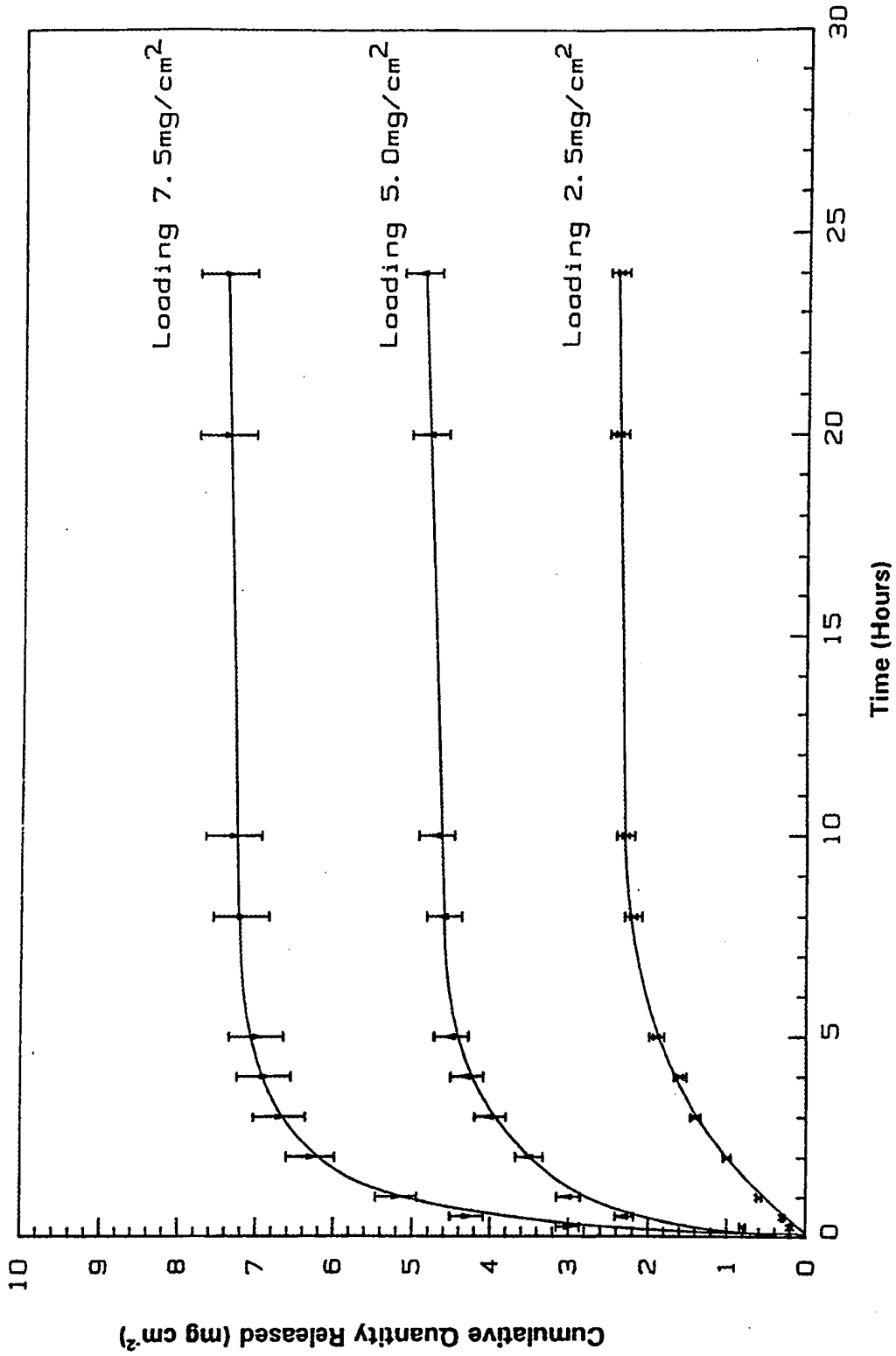

Cumulative Quantity Released (mg cm-2)
0
1
2
3
4
5
6
Time (Hours)
0
5
10
15
20
25
30
Adhesive 1 (polyisobutylene)
Adhesive 2 (acrylic)
Adhesive 3 (acrylic)
Adhesive 4 (silicone)

Fig 4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Loading 2.5mg/cm2
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3
4
5
6
7
8
9
10
0
5
10
15
20
25
30

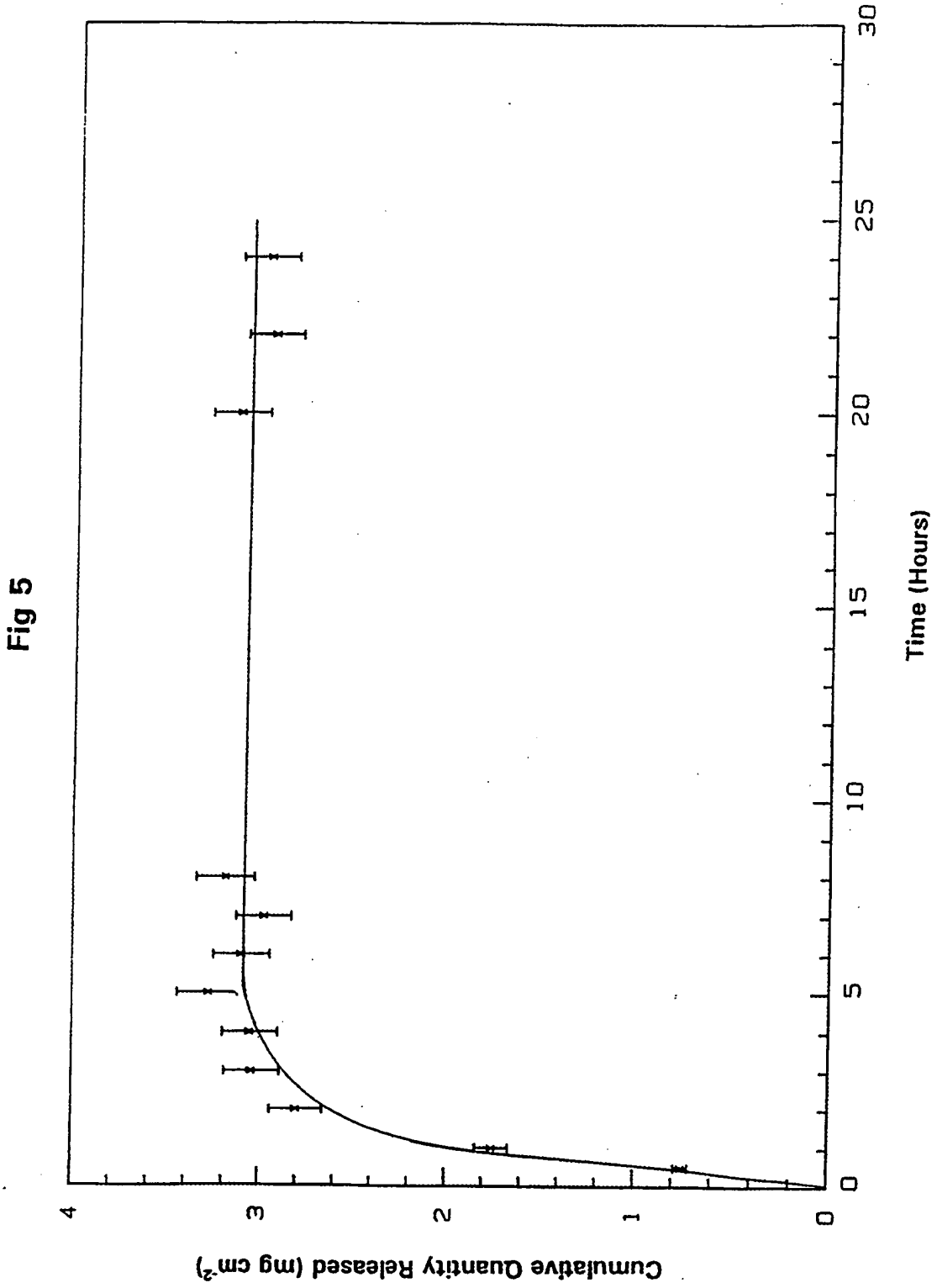
Cumulative Quantity Released (mg cm⁻²)
0
1
2
3
4
0
5
10
15
20
25
30
Time (Hours)

Fig 5

POLYMERIC BIOCHEMICAL COMPOSITIONS

This invention relates to polymeric biochemical compositions for medical and veterinary uses. In particular, the invention relates to polymeric biochemical compositions which contain an absorbed drug which, in use, is gradually released to the required site.

In one embodiment, the invention relates to a polymeric transdermal drug delivery composition for application to the skin. Transdermal drug delivery compositions are known. Such compositions are applied as a patch to the skin and contain pharmaceutical compound(s) which desorb from the composition in a controlled way, migrate transdermally and enter the blood stream of the patient. The composition thus acts as a reservoir for the impregnated drug.

According to the present invention a polymeric biochemical composition comprises a graft copolymer prepared from a substantially hydrophobic thermoplastic polymer irradiation-grafted with one or more substantially hydrophilic ethylenically unsaturated comonomers, the composition containing one or more pharmaceutical compounds. Optionally, the composition may contain additives such as fillers, plasticisers, thermal/oxidation stabilisers, dyes and pigments.

The graft copolymer itself is not new, but hitherto it has not been used to prepare polymeric biochemical compositions.

The thermoplastic polymer may be a polyolefin or a substituted polyolefin, such as polyethylene (which may be of any density - low, linear-low, medium or high density) or polypropylene, a polyamide, a polyetherurethane, a polyester or a copolymer of ethylenically unsaturated comonomers, for example an olefin and vinyl acetate. Copolymers of ethylene and vinyl acetate are preferred.

The substantially hydrophilic ethylenically unsaturated comonomer may be, in general, any reactive polar vinyl monomer, for example an ethylenically unsaturated acid such as acrylic acid or methacrylic acid, an ethylenically unsaturated carboxylic acid amide such as acrylamide, an ethylenically unsaturated carboxylic acid amine such as butylamine acrylate, or an organic base such as vinyl pyrrolidone or vinyl pyridine. Acrylic acid or an alkyl substituted acrylic acid, especially methacrylic acid, is preferred.

The graft copolymer is prepared by irradiation grafting of the thermoplastic polymer in the presence or absence of the comonomer and subsequent contact and reaction at elevated temperature with the comonomer if this is not present initially. Irradiation grafting is a well established technique in which the grafting of thermoplastic polymer is initiated by ionising radiation which produces active sites within the polymer bulk thus enabling the preparation of uniform, homogeneously grafted copolymers. Irradiation grafting can be achieved by

(a) mutual irradiation in which the thermoplastic polymer is irradiated in the presence of the comonomer, or

(b) post-irradiation grafting in which the thermoplastic polymer is irradiated and subsequently contacted with the comonomer.

Graft copolymers prepared by the post-irradiation method are preferred in the compositions of the present invention. In either method of irradiation grafting, the grafting reaction is normally carried out in the presence of an inhibitor to minimise undesirable homopolymerisation of the comonomer since homopolymer adversely affects the processability of the resultant graft copolymer. Examples of such inhibitors are ferrous sulphate, ammonium ferrous sulphate, cupric sulphate, cupric chloride, potassium ferricyanide and potassium dichromate. The preferred inhibitor is ferrous sulphate which advantageously is used at a concentration of 0.01 M to 0.2 M with respect to the grafting solution. The degree of grafting is preferably 10% to 50% by weight. This is calculated from the weights of the original thermoplastic polymer and the graft copolymer as shown below.

$$\% \text{ Graft} = \frac{\omega_f - \omega_i}{\omega_f} \times 100$$

where ω_f is the weight of grafted copolymer powder, and
ω_i is the initial weight of the copolymer powder.

In the post-irradiation method of grafting, the thermoplastic polymer to be grafted may be in particulate form, such as powder, pellet, flake, crumb or staple fibre. Powder having a grain size of 5 to 1000 μm diameter is preferred in order to obtain a uniform dispersion of the grafted monomers. Radicals are produced in the bulk of the polymer by exposure to ionising radiation in the presence of atmospheric oxygen. Typically, the radiation dose may be 0.5 to 100 KGy and the dose rate 0.5 to 5 KGy hr^{-1}. The irradiated and peroxidised polymer may be stored for an extended period of time, at room temperature, until required for grafting. The graft

copolymerisation may be effected by mixing the peroxidised polymer with a grafting solution comprising the monomer(s), demineralised water and homopolymerisation inhibitor (such as ferrous sulphate) which has been previously de-oxygenated and the reaction is carried out in the absence of oxygen. The monomer concentration in the grafting solution may be between 5% to 50% by weight and the homopolymerisation inhibitor may be at a concentration of 0.01 M to 0.2 M in the solution. To effect grafting, the reaction mixture is heated to an elevated temperature sufficient to decompose the radicals and the grafting reaction is continued until the required degree of graft copolymerisation is achieved. The copolymer is then removed from the reaction mixture by filtration and is washed and dried.

One advantage of the post-irradiation grafting process is that the copolymer preparation and processing may be carried out in bulk and the copolymer product is suitable for compounding and further processing by, for example, extrusion, injection or blow or compression moulding in the case of particulate copolymer, or lay up (wet or dry) or nonwovens from fibrous graft copolymers, by means known to those in the art. Thus the copolymers are readily compounded with compounding ingredients and pharmaceutical compounds to form the polymeric biochemical compositions of the invention, which are easy to form into transdermal drug delivery patches for application to the skin.

One example of a transdermal patch is shown schematically in Figure 1. It comprises an impermeable backing layer [1], the drug-containing copolymer of the invention [2] which is coated on both sides with an adhesive [3] and a release liner [4].

In use, the backing layer [1] is further from the skin and functions to prevent unwanted outward migration or evaporation of the drug from the patch. Suitable materials are commercially available and, for example, are made from polyester, polyvinylidene chloride and may be metallised and pigmented to skin colour.

The drug-containing layer [2] comprises the biochemical composition of the invention in the form of a permeable membrane, into which is compounded or absorbed a pharmacologically active substance or substances, for example nicotine, together with any skin permeation enhancing agents, diluents or surfactants which may be desirable and which are known to those practised in the art. Typical enhancing agents derive from polyalkylene glycols, polyalkylene glycol monolaurates, mono-, di- and tri-hydric alcohols and their monolaurate derivatives, isopropyl myristate, propionic acid and oleic acid.

The membrane is coated on both sides with an adhesive [3] which satisfies the criteria for use in transdermal delivery applications, in that it should be hypo-allergenic, discourage excessive migration of any of the constituents during storage, be chemically unreactive with the aforesaid constituents and provide comfortable and sufficient adhesion throughout the anticipated period of application. Typical examples of such adhesives are available commercially and are based upon acrylics, silicones or polyisobutylene.

The release liner [4] functions to prevent migration of the constituents and to preserve the cleanliness of the skin-contacting surface of the patch during storage and prior to application. Some typical materials which are suitable for this purpose include films of polyester, polyethylene and metal foils.

Figure 2 shows typical rates of in-vitro desorption of nicotine for graft copolymer membranes of the invention without adhesive.

Figure 3 compares typical rates of in-vitro desorption of nicotine for a graft copolymer membrane of the invention coated with acrylic, silicone and polyisobutylene adhesives.

Figure 4 illustrates the typical in-vitro desorption rates of a graft copolymer membrane of the invention as a function of the initial loading of nicotine.

Figure 5 illustrates the typical in-vitro desorption rate of ibuprofen for a graft copolymer of the invention without adhesive.

In the case of nicotine therapy, the amount of nicotine present is typically 7.5% to 30% by weight of the membrane.

In addition to its use in nicotine anti-smoking therapy, other application of the invention are as transdermal delivery reservoirs for anti-histamines, hormonal treatments, non-steroid anti-inflammatories, (eg ibuprofen), cardio-vascular treatments, (eg nitroglycerine, clonidine, propanolol, cardizerm), dermatological treatments, (eg colchicine), contraceptive therapy, vitamins, cosmetics and disinfectants. Examples of other uses are as ocular inserts, subcutaneous implants (eg for contraceptive purposes), catheters, enzyme immobilisation matrices for diagnostic processes and veterinary uses, eg vaginal rings.

Example 1

Ethylene-vinyl acetate copolymer powder, supplied under the trademark

EVATANE 1020VN5 with 18% vinyl acetate content, a melt flow index of 2 g/10 min measured according to ASTM D1238 and with an average particle size of 400 μm, was peroxidised by irradiation from a 370 TBq ^{60}Co source to a total dose of 25 KGy. 200 g of peroxidised ethylene-vinyl acetate copolymer powder was added to an aqueous acrylic acid solution containing 1 litre of deionised water, 5.56 g of ferrous sulphate heptahydrate (a homopolymerisation inhibitor) and 100 ml of acrylic acid. The mixture was deoxygenated by bubbling with oxygen-free nitrogen for a period of 2 hours. The reaction mixture was placed in a thermostatted water bath and stirred under nitrogen for 3 hours at a temperature of 80°C. The grafted copolymer powder mixture was filtered from the grafting solution, washed thoroughly with warm deionised water and dried to constant weight. The dried grafted copolymer powder was then weighed and the degree of grafting was found to be 26%. The degree of grafting was calculated as follows:

$$\% \text{ Graft} = \frac{\omega_f - \omega_i}{\omega_f} \times 100$$

where ω_i was the initial weight of the copolymer powder, and

ω_f was the resultant weight of the grafted copolymer powder.

Example 2

A sample of ethylene-vinyl acetate grafted copolymer powder, prepared as in Example 1, was compounded and extruded into sheet film of 200 μm

thickness and 300 mm in width at a rate of 1.6 m min^{-1}. The processing parameters for the grafted copolymer powder were as follows:

Screw Speed	32 rpm
Zone 1	144°C
Zone 2	157°C
Zone 3	145°C
Chill Roll	Cooled by water circulation
Air Gap	10 mm
Necking	40 mm

Samples of the extruded films were cut into 10 cm^2 pieces. The samples were weighed and immersed in 750 ml of an impregnating solution of 5% w/w nicotine in water, maintained at 37°C for 2½ hours. The impregnated film was then placed between two sheets of absorbent tissue, fed through two rollers applying a constant pressure, and dried in an air circulating oven at 23°C. The nicotine content of the impregnated film was determined by soxhlet extraction of the film in ethanol, followed by analysis of the ethanol extract using a UV spectrophotometer at 260 nm.

The properties of the nicotine impregnated film, which contained 5 mg of nicotine/cm^2, were determined by carrying out desorption studies at 37°C. The results are illustrated by Curve 1 in Figure 2, which shows the cumulative quantity of nicotine released per cm^2 as a function of time.

Example 3

175 g of ethylene-vinyl acetate copolymer powder was placed into a 2 litre flange-necked flask. The grafting solution containing 50 ml of acrylic acid, 8.0 g of ferrous sulphate heptahydrate, 950 ml of deionised water was added and the mixture was purged with oxygen-free nitrogen for several hours. The mixture was then irradiated using a ^{60}Co gamma irradiation source to a total irradiation dose of 5 KGy at a dose rate of 0.6 KGy hr^{-1}, and at room temperature. The grafted copolymer mixture was filtered off the grafting solution, washed thoroughly with warm deionised water and dried. The degree of grafting of the copolymer powder was found to be 20%.

The powder was extruded into film, impregnated with nicotine, cut into pieces and tested for nicotine desorption properties according to the methods of Example 1. The results obtained are illustrated by Curve 2 in Figure 2.

Example 4

Samples of the extruded membrane film of Example 2 were cut into 12.5 cm^2 pieces, weighed and immersed into 750 ml of aqueous solutions of nicotine at concentrations of 1.5%, 2% and 5% w/w, maintained at 37°C for 2½ hours. After drying the impregnated pieces were measured for total nicotine content and were found to be 56.00 mg, 62.94 mg and 63.25 mg respectively.

Example 5

Samples of the film, extruded and impregnated by the methods of Example 2, measured to have a nicotine loading of 5 mg cm^{-2}, were coated with polyisobutylene, a silicone-based and two acrylic-based adhesives, all at the 5 g m^{-2} coating weight. The in-vitro desorption of nicotine at 37°C was measured and the cumulative quantities with time are shown in Figure 3.

Example 6

Samples of the extruded film of Example 2 were cut into 20 cm^2 pieces and impregnated with nicotine at loadings of 2.5 mg cm^{-2}, 5.0 mg cm^{-2} and 7.5 mg cm^{-2}. In-vitro desorption studies yielded the results shown in Figure 4.

Example 7

The grafted copolymer powder of Example 1 was intimately blended with ibuprofen and propylene glycol in the proportions 10:1:2 w/w respectively. The resulting mixture was extruded into sheet film of thickness 300 μm. Samples of the extruded film were cut into 20 cm^2 pieces and weighed. The ibuprofen content was determined as 60 mg cm^{-2} by soxhlet extraction of the pieces in ethanol followed by spectrophotometric analysis of the eluate at 264 nm. In-vitro desorption studies at 37°C for the rate of ibuprofen release yielded the results illustrated in Figure 5.

Claims

1. A polymeric biochemical composition comprising a graft copolymer prepared from a substantially hydrophobic thermoplastic polymer irradiation-grafted with one or more substantially hydrophilic ethylenically unsaturated comonomers, the composition containing one or more pharmaceutical compounds.

2. A composition according to Claim 1, in which the graft copolymer is prepared by irradiation grafting a polyolefin, a polyamide, a polyether urethane, a polyester or an olefin-vinyl acetate copolymer with the hydrophilic comonomer(s).

3. A composition according to Claim 1 or Claim 2 in which the hydrophilic comonomer(s) is/are selected from an ethylenically unsaturated acid, an ethylenically unsaturated carboxylic acid amide, an ethylenically unsaturated carboxylic acid amine, vinyl pyrrolidone or vinyl pyridine.

4. A composition according to any one of Claims 1 to 3 in which the graft copolymer is an ethylene-vinyl acetate polymer grafted with acrylic and/or methacrylic acid.

5. A composition according to any one of the preceding claims in which the graft copolymer is prepared by post irradiation grafting in which the thermoplastic polymer is irradiated and subsequently contacted with the comonomer(s).

6. A composition according to any one of the preceding claims in which the thermoplastic polymer is in the form of a powder having a grain size of 5 to 1000 μm diameter.

7. A composition according to any one of the preceding claims formed to provide the reservoir matrix of a controlled release device.

8. A composition according to Claim 7, in which the device is a transdermal drug delivery patch for application to skin, an ocular insert, an implant, an enzyme immobilisation matrix for diagnostic processes or a vaginal ring.

9. A transdermal drug delivery patch according to Claim 8, in which the pharmaceutical compound is nicotine.

10. A pharmaceutical composition substantially as herein before described with reference to and as shown in the examples and the accompanying drawings.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (Search report)	Application number GB 9321687.7
Relevant Technical Fields (i) UK Cl (Ed.L) A5B (BJC, BKE, BLG, BLM) C3V (VET) (ii) Int Cl (Ed.5) A61K 47/32, 47/34	Search Examiner J F Jenkins Date of completion of Search 28 January 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES : WPI, CAS-ONLINE	Documents considered relevant following a search in respect of Claims :- 1 to 10

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

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P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
A	GB 2035350 A	(P J FYDELOR et al) see Claims 1 to 7 and 11; page 2 lines 23-43	
E	US 5262484	(COLEMAN et al) see Claims 1 to 3, 11 to 14	
X	US 4283325	(BERTHET et al) see Examples 1 to 9, Claims 1-20	1-8
X	GB 1456775	(APAMED ANSTALT)	1-5 & 8

Databases:The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).